J Orthopaed Traumatol (2006) 7:187–191
DOI 10.1007/s10195-006-0146-5

ORIGINAL

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Time course of thrombosis and fibrinolysis during total hip surgery

Received: 23 August 2006
Accepted: 31 October 2006
Published online: 18 December 2006

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Abstract Venous thrombosis is common in elective hip surgery, and prophylactic treatment is used up to 12 hours before or after surgery. Recent clinical trials suggested that the timing of initiating prophylaxis significantly influenced the antithrombotic effectiveness. Furthermore, the timing of initiating antifibrinolytic treatment to reduce blood loss has been a question of debate. We studied the time course of coagulation and fibrinolysis at all phases during total hip arthroplasty. Specific markers of thrombosis (prothrombin fragment F1.2) and of fibrinolysis (plasmin-antiplasmin (PAP) and D-Dimer) were examined in eight female and two male patients aged 16–62 years. There was a progressive increase in plasma concentrations of F1.2 during the operation. From the end of operation to 4 hours afterwards, there was no further increase in F1.2. Levels of D-Dimer did not change until wound closure, when they began to increase up to 4 hours postoperatively, but there were no changes in PAP during the operation or during the 4-h postoperative period. Therefore, surgery for total hip arthroplasty activates thrombin generation during operation with fibrin degradation at a later stage. These observations harmonize with the notion that the interval between surgery and first administration of antithrombotic treatment is a critical variable.

Key words Arthroplasty • Anticoagulation • Fibrinolysis • Orthopaedic surgery • Thrombosis

Introduction

Venous thrombosis is common in high-risk surgical patients and occurs in 40%–60% of patients undergoing total hip arthroplasty (THA) in the absence of thromboprophylaxis [1, 2]. Clinical practice regarding initiation of antithrombotic prophylaxis in surgery differs. In Europe, it is recognized that deep vein thrombosis originates perioperatively and that preoperative prophylaxis may optimize antithrombotic effects [3–7]. Low-molecular-weight heparin (LMWH) is usually initiated 12 hours preoperatively [8–21]. In North America, LMWH prophylaxis is started 12–24 hours postoperatively to minimize bleeding risk [22–26], and there have also been concerns about spinal hematomas related to the practice of neuraxial anesthesia and use of LMWH prophylaxis [27, 28]. However, the risk of bleeding associated with prophylaxis for venous thromboembolism (VTE) varies depending on the type and dose of prophylactic medication. Because of differences in methods of reporting, the small size of many studies, and the infrequency of postoperative bleeding complications, meaningful conclusions cannot be drawn as to whether deferring VTE prophylaxis until after surgery appreciably reduces operative blood loss or subsequent bleeding.

In orthopaedic surgery, blood loss can be quite substantial. To minimize bleeding, fibrinolytic inhibitors like tranexamic acid have been used in total hip replacement, and lower blood loss has been reported [29–32]. However, the timing and administration of tranexamic acid varies in the different studies, and there seems to be no consensus.

In light of controversies regarding the timing of thromboprophylaxis regimens and the administration of tranexamic acid, we investigated the time course of thrombosis and fibrinolysis during total hip replacement as a major musculoskeletal operation.

Patients and methods

The study enrolled 8 female and 2 male patients who underwent primary THA with insertion of an uncemented prosthesis (Landos stem and Harris Galante cup). The patients were unselected and, except for one who had chronic obstructive pulmonary disease, they were otherwise healthy. The study was approved by the regional committee on ethics and was performed in accordance with the ethical standards of the Declaration of Helsinki; written informed consent was obtained from all patients.

Anesthesia was standardized with spinal/epidural injections at the lumbar level with 5 mg/ml bupivacaine (Marcain; AstraZeneca, Södertälje, Sweden). Postopertively, 2.5 mg/ml bupivacaine combined with 0.05 mg/ml fentanyl were used epidurally.

Thromboprophylaxis was given as subcutaneous injections of 5000 IU LMWH (dalteparin, Fragmin; Pfizer, New York, USA) the evening before surgery and thereafter daily. Antibiotic prophylaxis was given as 2 g cefalotin (Keflin; EuroCept Pharmaceuticals, Kortenhoef, Holland) intravenously, three times in one day.

Blood samples were drawn from an arterial cannula at the following time points: control values before surgery, after section of the femoral neck, after reaming of the femoral medullary cavity, 30 min after reaming, at wound closure and 4 h after surgery. Plasma was separated by centrifugation at 2500g for 20 min at 18° C and stored at -80° C until assayed.

Prothrombin fragment F1.2 was measured in citrated plasma by ELISA using a commercial kit (Enzygnost F1+2 micro; Dade Behring, Marburg, Germany). Plasmin/α2-antiplasmin (PAP) complex was measured in citrated plasma by ELISA using a commercial kit (Enzygnost PAP micro, Dade Behring). D-Dimer was determined in citrated plasma using a commercial kit (STA-Liatest D-Di; Diagnostica Stago, Asnières s/Seine, France).

Time-dependent changes were analyzed on Friedman's nonparametric test for related samples. When significant differences were found, the Wilcoxon signed rank test was used. The level of significance was set at p=0.05.

Results

We studied coagulation and fibrinolysis during THA in 10 patients aged 16–62 years. Patient demographics, comorbidity, duration of surgery, blood loss, autotransfusion of blood and saline and colloid replacements are given in Table 1.

There was a steady increase in prothrombin fragment F1.2 during surgery (p=0.023) (Table 2). However, from the end of surgery to 4 hours postoperatively, there was no significant change in F1.2 (p=0.499). D-Dimer concentration was unchanged until wound closure when there was a significant increase until 4 hours after surgery (p=0.002). During the course of surgery and up to 4 hours postoperatively, there were no significant changes in levels of PAP (p=0.288).

Table 1 Clinical and operative characteristics of 10 patients who underwent total hip arthroplasty

Patient	Sex	Age, years	Comorbidity	Surgery duration, min	Blood loss, ml	Auto-transfusion, ml	Saline transfusion, ml	Colloids, ml
1	F	39	–	120	1000	300	3200	1000
2	F	38	–	80	600	210	2100	500
3	M	17	–	95	1000	–	1500	500
4	F	62	COPD	125	700	214	2000	500
5	F	38	–	120	400	–	2500	500
6	M	16	–	63	300	–	1100	–
7	F	43	–	96	400	–	1250	500
8	F	61	–	100	1000	242	2000	100
9	F	24	–	95	500	–	2000	500
10	F	48	–	110	600	–	2500	500

COPD, chronic obstructive pulmonary disease

Table 2 Prothrombin fragment F1.2, D-Dimer and plasmin-antiplasmin (PAP) complex during and after total hip replacement surgery. Time points are (1) before anesthesia, (2) after section of the femoral neck, (3) after reaming of the femoral medullary cavity, (4) 30 min after reaming, (5) at wound closure, and (6) 4 hours after surgery. Median and interquartile ranges are given

Time point	F1.2 (pmol·mL^{-1})	D-dimer (μg·mL^{-1})	PAP (μg·L^{-1})
1	220 (188–240)	0.09 (0.06–0.28)	930 (368–1302)
2	280 (233–391)*	0.17 (0.07–0.27)	884 (396–967)
3	395 (228–699)‡	0.21 (0.13–0.39)	872 (508–113)
4	418 (347–757)‡	0.51 (0.30–0.99)	812 (419–1141)
5	600 (429–713)‡	1.70 (1.19–3.00)‡	815 (494–1471)
6	565 (500–1034)#	3.76 (2.04–7.08)§	806 (509–1063)
p (ANOVA)	0.023	0.002	0.288

*p=0.021, ‡p=0.012, #p=0.008, §p=0.018 vs. values at time point 1

Discussion

In this study, markers of thrombosis and fibrinolysis were measured during the different phases of THA. We found that intravascular thrombin formation originated at the start of surgery, and that activation was at a maximum at the end of surgery. Thrombin formation is a key regulatory step in surgical hemostasis. The short half-life of active thrombin precludes direct measurements. However, by conversion of prothrombin to thrombin, the amino terminal of prothrombin is cleaved to generate the inactive F1.2 fragment which is a sensitive marker of prothrombin activation and thrombin generation [33]. Our observations harmonize with the understanding that the risk of thrombosis starts perioperatively.

A previous study [34] reported that the greatest activation of the clotting cascade was during insertion of the femoral component. However, this was more pronounced after insertion of a cemented rather than a noncemented stem. This may be explaned by the fact that when a cemented stem is impacted, tissue thromboplastin from the bone and bone marrow is forced into the circulation; when cement is not used, there is less release of tissue thromboplastin. Therefore, we used uncemented THA as a model for thrombin generation during an orthopaedic operation. It may be argued that there was a rather great dispersion of age and a skewed distribution of sexes in our patients. However, the changes in markers during the experimental period were not related to age or gender of the patients (data not shown).

A factor contributing to deep vein thrombosis during total hip arthroplasty may be femoral vein occlusion during surgery [34]. In general, venous occlusion triggers thrombosis. When the hip and leg are flexed and rotated, the femoral vein is twisted and kinked, and femoral vein occlusion then may trigger thrombosis. Although femoral vein occlusion may be an important component in the genesis of deep vein thrombosis during surgery on the lower extremities, our data do not suggest that it by itself was sufficient to activate markers.

Seconday to thrombin generation, fibrinolysis is activated by plasminogen activator. Plasmin acts on cross-linked fibrin to generate d-dimers [35], and through its activation plasmin binds to with α_2-antiplasmin inhibitor to form the plasmin-antiplasmin complex. We measured D-Dimer and PAP as indicators of plasmin activity. Significant degradation of fibrin was found at wound closure with further increases up to 4 hours postoperatively. On the other hand, there was no increase in PAP. These observations concur with previous findings that fibrinolytic activity is enhanced intraoperatively with a shutdown after surgery [36]. The postoperative fibrinolytic shutdown was ascribed to a temporary increase in t-PA inhibitor levels after surgery.

The use of tranexamic acid to reduce bleeding in total hip replacement surgery has been debated, and the timing and dosage are controversial [32]. Tranexamic acid acts by inhibiting the activation of plaminogen to plasmin. However, we found no significant increases in PAP during and up to 4 hours after surgery. Our results, then, reflect that systemic use of tranexamic acid to reduce blood loss during THA may be questioned.

Changes of markers during high-risk surgery are difficult to translate into a recommendation of timing for thromboprophylaxis. However, increased plasma concentrations of F1.2 and D-Dimer were found to correlate with thrombosis [33, 37], and our results support the view that the interval between surgery and the first administration of prophylaxis is a critical variable that

may influence the occurrence of deep vein thrombosis in patients undergoing elective hip arthroplasty [38]. Thromboprophylaxis in close proximity to hip arthroplasty, either preoperatively or postoperatively, may balance efficacy and safety to prevent thrombosis on one hand and bleeding on the other hand. Clinical observations indicated that LMWH at half the usual high-risk dose begun in close proximity to THA either preoperatively or postoperatively [39, 40] was more effective than LMWH administered 12 hours preoperatively or 12–18 hours postoperatively [17, 19]. However, administration less than 2 hours before surgery resulted in increased major bleeding, while a postoperative regimen of LMWH 4–6 hours after surgery provided efficacy without significantly increasing bleeding [40].

In conclusion, our analysis indicates that activation of thrombin generation and fibrinolysis starts during surgery of THA. The interval between surgery and first administration of antithrombotic treatment, then, is a critical variable in musculoskeletal operations with pathophysiological evidence for the initiation of anticoagulation during or immediately after surgery.

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